# Exhibit 3

Patents

# Method for synthesizing valsartan


## Abstract

A method for synthesizing valsartan, comprising the steps of: synthesizing a valsartan methyl ester intermediate to obtain a reaction mixture of the valsartan methyl ester intermediate; diluting the reaction mixture by salt water or water, and then using a first extraction solvent to extract the valsartan methyl ester intermediate; adding alkali to an organic layer containing the valsartan methyl ester intermediate for hydrolyzing, removing the organic layer, regulating pH of a water layer to be acidic by using acid, using the first extraction solvent to extract, concentrating a part of solvent, or distilling the solvent to dryness, and then adding a new solvent; finally, crystalizing, filtering, and drying to obtain the valsartan. The synthesization method provided in the present invention can avoid from the process source the possibility that highly toxic impurities such as N-nitrosodimethylamine (NDMA), a valsartan impurity K, and valsartan N-chloride generated in the azide quenching process are introduced into the valsartan methyl ester intermediate, and are further introduced into the valsartan active ingredient, thereby ensuring the valsartan medication safety.


## Classifications

- C07D257/04 Five-membered rings


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WIPO (PCT)

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**Other languages:** French, Chinese

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## Claims (17)

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1. A method for synthesizing valsartan, characterized in that the prepared valsartan does not contain N-nitrosodimethylamine, valsartan impurity K, and valsartan N-chloride; the method includes the following step:

   (1) synthesizing a valsartan methyl ester intermediate to obtain a reaction mixture containing the valsartan methyl ester intermediate;

   Preferably, the step (1) comprises: dissolving valsartan cyanide intermediate in N, N-dimethylformamide, then adding azide and first acid, heating and stirring to form tetrazolium Ring reaction to synthesize valsartan methyl ester intermediate to obtain a reaction mixture containing valsartan methyl ester intermediate;

   (2) Dilute the reaction mixture with saline or water, add a first extraction solvent, and heat extract the intermediate of valsartan methyl ester; stand still and separate the layers to separate the aqueous layer to obtain valsartan methyl ester The first organic layer of the intermediate; washing the first organic layer at least once with brine or water, separating the aqueous layer to obtain a second organic layer containing the valsartan methyl ester intermediate;

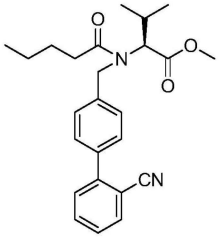
   Preferably, the water layers separated in step (2) are combined, and the azide in the separated water layer is quenched with a quencher under acidic conditions;

   (3) adding an alkali solution to the second organic layer containing the valsartan methyl ester intermediate, hydrolyzing with stirring, standing still to separate the layers, and after separating the organic layer, adjusting the pH of the aqueous layer to acidic with a second acid, Then add a second extraction solvent to the aqueous layer to extract the valsartan compound; stand still and layer to obtain a third organic layer containing the valsartan compound; control the third organic layer by adding a desiccant or distilling away water The moisture content is lower than the target value; when the solvent in the third organic layer is partially concentrated, or the solvent in the third organic layer is evaporated, and a new solvent is added, the crystal is crystallized and filtered to obtain the crude valsartan;

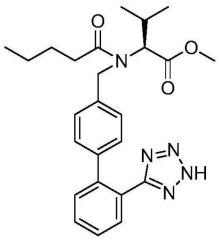
   Preferably, the target value is 2% by mass, preferably 1%, more preferably 0.5%, and most preferably 0.35%;

   (4) adding the crude valsartan to a crystallization solvent, heating to dissolve, holding the crystals after cooling, filtering, filtering, washing and drying the filter cake with the crystallization solvent to obtain a finished valsartan;

   The structures of the valsartan cyanide intermediate and the valsartan methyl ester intermediate are respectively the following formula I and formula II:

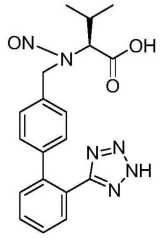


式 I



式 II。

2. The method according to claim 1, wherein the structure of the valsartan impurity K is as follows:



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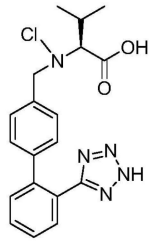
The structure of the valsartan N-chloro compound is as follows:



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3. The method according to claim 1 or 2, wherein the azide in step (1) is selected from the group consisting of sodium azide, potassium azide, lithium azide, cesium azide, and trimethyl azide. One or any combination of silicon azides;

Preferably, the azide is selected from sodium azide, potassium azide, or trimethylsilyl azide.

4. The method according to any one of claims 1 to 3, wherein the first acid in step (1) is a Lewis acid; preferably, the first acid is selected from triethylamine hydrohalic acid Salt, triethylamine sulfate, triethylamine hydrogen sulfate, triethylamine phosphate, triethylamine hydrogen phosphate, trimethylamine hydrohalide, trimethylamine sulfate, trimethylamine hydrogen sulfate, trimethylamine phosphate , Trimethylamine hydrogen phosphate, diisopropylethylamine hydrohalide, diisopropylethylamine sulfate, diisopropylethylamine hydrogen sulfate, diisopropylethylamine phosphate, pyridine hydrohalide Salt, pyridine sulfate, pyridine hydrogen sulfate, pyridine phosphate, pyridine phosphate, N-methylmorpholine hydrohalide, N-methylmorpholine sulfate, N-methylmorpholine hydrogen sulfate, N-methylmorpholine phosphate, N-methylmorpholine hydrogen phosphate, N-methylpiperidine hydrohalide, N-methylpiperidine sulfate, N-methylpiperidine hydrogen sulfate, N -Methylpiperidine phosphate, N-methylpiperidine hydrogen phosphate, N-methyltetrahydropyrrole hydrohalide, N-methyltetrahydropyrrole sulfate, N-methyltetrahydropyrrole sulfate N-methyltetrahydropyrrole Acid, N- methyl pyrrolidine hydrogen phosphate, tributyl tin chloride, anhydrous zinc chloride, zinc chloride dihydrate, anhydrous titanium tetrachloride in one kind, or any combination thereof;

More preferably, the first acid described in step (1) is selected from the group consisting of triethylamine hydrogen chloride, triethylamine sulfate, triethylamine hydrogen sulfate, pyridine hydrochloride, or anhydrous zinc chloride.

5. The method according to any one of claims 1-4, wherein the temperature range of the tetrazolium ring-forming reaction in step (1) is 70-180 ° C; and the preferred reaction temperature range is 100-140 ° C. .

6. The method according to any one of claims 1-5, wherein the brine in step (2) is selected from the group consisting of an aqueous solution of sodium chloride, an aqueous solution of magnesium chloride, an aqueous solution of potassium chloride, an aqueous solution of calcium chloride, and sodium sulfate One of the aqueous solutions or any combination thereof;

   Preferably, the brine described in step (2) is a saturated sodium chloride aqueous solution or a 10-20% sodium chloride aqueous solution by mass.

7. The method according to any one of claims 1-6, wherein the first extraction solvent in step (2) is an organic solvent that can dissolve the valsartan methyl ester intermediate and is immiscible with water. Solvent

   Preferably, the first extraction solvent described in step (2) is selected from toluene, xylene, methylene chloride, methyl tert-butyl ether, isopropyl ether, n-butyl ether, anisole, phenyl ether, n-hexane One of ether, n-heptyl ether, or any combination thereof; more preferably, the first extraction solvent is selected from toluene, xylene, methyl tert-butyl ether, anisole, or n-butyl ether.

8. The method according to any one of claims 1 to 7, characterized in that the heating temperature during the heating extraction in step (2) ranges from 35 to 140 ° C, preferably from 45 to 100 ° C.

9. The method according to any one of claims 1 to 8, characterized in that the quencher is selected from one of nitrite, hypochlorite or hypobromite, or any combination thereof, preferably The ground is selected from one of sodium nitrite, potassium nitrite, sodium hypochlorite, sodium hypobromite, calcium hypobromite, calcium hypochlorite or any combination thereof, and more preferably selected from sodium nitrite or sodium hypochlorite.

10. The method according to any one of claims 1 to 9, characterized in that when quenching the azide in the water layer, the acid used to form acidic conditions is an inorganic strong acid, preferably one of hydrochloric acid and sulfuric acid Or a combination thereof; after the acid is added, the pH value is adjusted to be 0-5, preferably 1-3.

11. The method according to any one of claims 1 to 10, wherein the alkali solution in step (3) is one of a hydroxide aqueous solution and a carbonate aqueous solution, or a combination thereof, and preferably a mass A 30% aqueous sodium hydroxide solution or a 30% potassium hydroxide aqueous solution.

12. The method according to any one of claims 1 to 11, characterized in that, after adding the alkali solution in step (3), the hydrolysis reaction is performed with stirring, and the temperature of the hydrolysis reaction ranges from -10-40 ° C, preferably from 0-20 ° C. ;

    Preferably, the hydrolysis reaction time ranges from 5 to 40 hours, preferably from 15 to 25 hours.

13. The method according to any one of claims 1 to 12, characterized in that, in the step (3), the step of adjusting the pH of the water layer to an acidic state with a second acid, the second acid used is a strong inorganic acid, Preferably, it is one of hydrochloric acid and sulfuric acid or a combination thereof; the pH is adjusted in the range of 0.5-6, preferably 1-3 after adding acid.

14. The method according to any one of claims 1 to 13, characterized in that the second extraction solvent used in step (3) is a solvent that can be separated from the water layer, preferably ethyl acetate or methyl tert-butyl Based ether.

15. The method according to any one of claims 1 to 14, wherein the new solvent in step (3) is a single solvent or a mixture of multiple solvents capable of dissolving valsartan;

    Preferably, the new solvent is selected from ethyl acetate, acetone, ethanol, isopropanol or a mixed solvent of ethyl acetate and dichloromethane;

    More preferably, in the mixed solvent of ethyl acetate and dichloromethane, the volume ratio of ethyl acetate to dichloromethane is 1: 3 to 3: 1.

16. The method according to any one of claims 1 to 15, characterized in that the desiccant in step (3) is selected from one of an anhydrous metal chloride salt, an anhydrous metal sulfate salt, or a combination thereof. , Preferably selected from anhydrous magnesium sulfate or anhydrous sodium sulfate.

17. The method according to any one of claims 1 to 16, wherein the crystallization solvent in step (4) is a single solvent capable of dissolving valsartan and a mixture of multiple solvents, preferably ethyl acetate. Or a mixed solvent of ethyl acetate and dichloromethane;

    More preferably, in a mixed solvent of ethyl acetate and dichloromethane, the volume ratio of ethyl acetate to dichloromethane is 1: 3 to 3: 1.

## Description

Synthesis method of valsartan

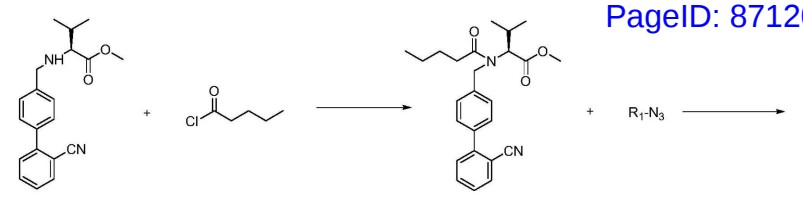
This application claims priority from a Chinese patent application filed with the Chinese Patent Office on July 13, 2018, with an application number of 201810771261.1, entitled "A Synthetic Method of High-Purity Valsartan," the entire contents of which are incorporated herein by reference Applying.

**Technical field**

The invention relates to the technical field of medicines, in particular to a method for synthesizing valsartan.

**Background technique**

Valsartan is a widely used antihypertensive drug in clinical practice. It has the advantages of small side effects and good tolerance, and can also be used for the treatment of hypertension in patients with diabetes and kidney disease. The pharmacophore in the valsartan molecule is biphenyltetrazole. In the production of commercial products, the most common construction strategy for the tetrazolium ring is to synthesize it with cyanobiphenyl and azide at high temperature. The general commercial production route of such valsartan is expressed as follows:



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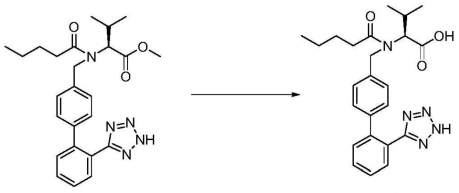

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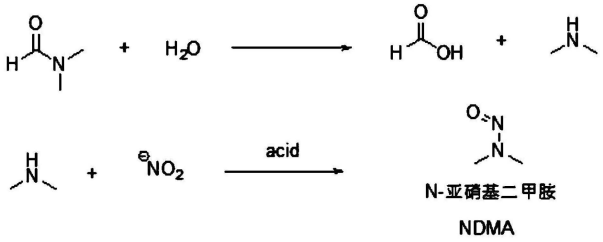
$R_1$ represents a group such as Na, K or TMS.

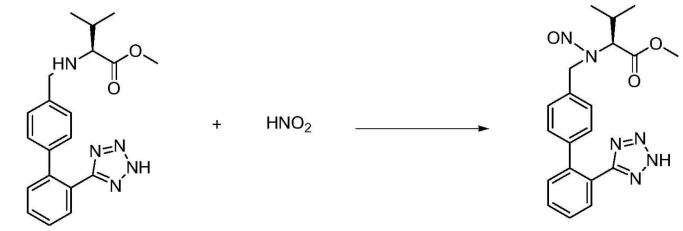
In the above synthesis route of valsartan, the most suitable solvent in the tetrazolium cyclization step is N, N-dimethylformamide (DMF); this is because DMF has excellent solubility and relatively high With boiling point and DMF as the solvent, the conversion substrate valsartan cyanide has the highest conversion rate, the palmar molecules in the reaction substrate are the most stable in DMF solvents under high temperature conditions and are not easy to racemate to produce isomer impurities. At the same time, in commercial production, in order to ensure that the valsartan cyanide intermediate is fully converted during the reaction, azide reactants such as sodium azide, potassium azide or $TMSN_3$ are used in the reaction in excess; After the reaction, if the azide is not quenched, toxic azide acid will be generated in the subsequent processes; at the same time, the material containing azide is in contact with materials containing copper or other transition metal materials during the transfer process. Explosions are prone to occur; therefore, in order to ensure the safety of operation, the residual azide compounds in the process must be quenched by using nitrite to destroy the residual azide under acidic conditions.

Summary of the invention

The inventor of the present application discovered during the development of the valsartan synthesis process that when DMF is used as a solvent, DMF is easily decomposed to generate dimethylamine during a high-temperature reaction. During the azide quenching process, dimethylamine Will react with nitrite to produce highly toxic N-nitrosodimethylamine (NDMA) impurities. If the valsartan methyl ester intermediate in the valsartan process is not first separated, the N- Nitrodimethylamine (NDMA) impurities will remain in the valsartan drug substance. The process of NDMA production is as follows:




In addition, patent document CN103613558A also states that during the quenching of azide with nitrite under acidic conditions, a small amount of devaleryl impurities in the intermediate of valsartan methyl ester will react with nitrous acid to produce An N-nitroso compound will be converted into valsartan impurity K in the subsequent process. The process is as follows:



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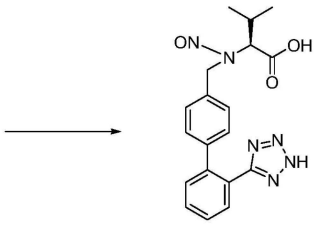

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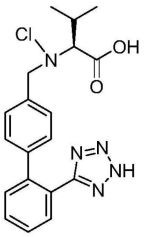
In this patent document, the improved strategy is to replace sodium nitrite with sodium hypochlorite to quench the azide; however, after further research by the inventor of this application, it is found that although the technical solution of this patent document can avoid the generation of impurity K, it It may also produce another highly toxic valsartan N-chloride impurity, whose structural formula is as follows:



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The inventors of the present application have further studied the synthesis process of valsartan and found that, before quenching the azide, the valsartan methyl ester intermediate is first separated, which can avoid the high Possibility of impurities such as toxic N-nitrosodimethylamine (NDMA), valsartan impurity K, and valsartan N-chloride to be incorporated into valsartan bulk drugs; further, by optimizing other operating conditions, For example, the moisture content in the solvent during crystallization, the crystallization temperature, and the like are controlled to prepare a valsartan product with high purity (without the above impurities); the present invention has been completed based on the above findings.

The purpose of the present invention is to provide a method for synthesizing high-purity valsartan to synthesize non-toxic N-nitrosodimethylamine (NDMA), valsartan impurity K, and valsartan N-chloride. Valsartan and other impurities, the method includes the following steps:

(1) synthesizing a valsartan methyl ester intermediate to obtain a reaction mixture containing the valsartan methyl ester intermediate;

In some specific embodiments of the present invention, the step (1) includes: dissolving valsartan cyanide intermediate in N, N-dimethylformamide (DMF), and then adding azide and first Monoacid, heating and stirring to carry out tetrazole ring-forming reaction to synthesize valsartan methyl ester intermediate, thereby obtaining a reaction mixture containing valsartan methyl ester intermediate;

(2) Dilute the reaction mixture with brine or water, add the first extraction solvent, and extract the valsartan methyl ester intermediate after heating; leave it to separate the layers and separate the aqueous layer to obtain the valsartan methyl ester intermediate. The first organic layer; washing the first organic layer at least once with brine or water, separating the aqueous layer to obtain a second organic layer containing a valsartan methyl ester intermediate;

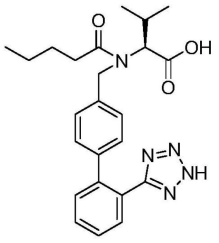
In some specific embodiments of the present invention, the water layers separated in step (2) may be combined, and a quenching agent may be used to quench the azide in the separated water layers under acidic conditions;

(3) adding an alkali solution to the second organic layer containing the valsartan methyl ester intermediate, hydrolyzing with stirring, standing still to separate the layers, and after separating the organic layer, adjusting the pH of the aqueous layer to acidic with a second acid, Then add a second extraction solvent to the aqueous layer to extract the valsartan compound, and stand still and layer to obtain a third organic layer containing the valsartan compound; control the third organic layer by adding a desiccant or distilling water away The moisture content is lower than the target value; when the solvent in the third organic layer is partially concentrated, or the solvent in the third organic layer is evaporated, and a new solvent is added, the crystal is crystallized and filtered to obtain the crude valsartan;

In some specific embodiments of the present invention, the target value is 2% by mass, preferably 1%, more preferably 0.5%, and most preferably 0.35%;

(4) The crude valsartan is added to a crystallization solvent, heated to dissolve, and cooled to keep the crystals, filtered, and the filter cake is washed with the crystallization solvent and dried to obtain a finished valsartan.

Valsartan mentioned in the present invention has the following structural formula:



$C_{24}H_{29}N_5O_3$
Exact Mass: 435.227

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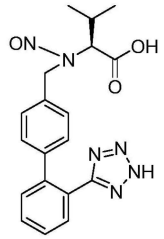
The N-nitrosodimethylamine (NDMA) mentioned in the present invention has a structural formula as follows:

N-亚硝基二甲胺

NDMA ;

The valsartan impurity K mentioned in the present invention has the following structural formula:



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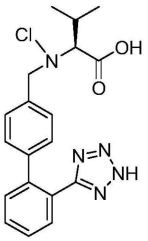
The valsartan N-chloro compound mentioned in the present invention has the following structural formula:



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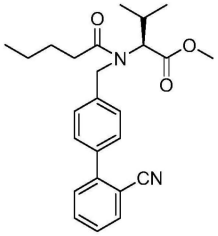
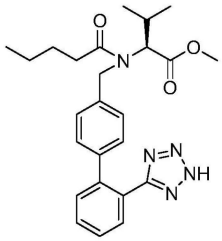
In the present invention, the structural formula of the valsartan cyanide intermediate is shown as I:



式 I;

In the present invention, the structural formula of the valsartan methyl ester intermediate is shown in II:



式 II。

In some embodiments of the present invention, the azide in step (1) is selected from the group consisting of sodium azide, potassium azide, lithium azide, cesium azide, and trimethylsilazide (TMSN $_3$ ), Or any combination thereof; preferably selected from sodium azide, potassium azide, or trimethylsilazide (TMSN $_3$ ).

In some specific embodiments of the present invention, the first acid in step (1) is a Lewis acid; preferably, the first acid is selected from the group consisting of triethylamine hydrohalide, triethylamine sulfate, and triethylamine Hydrogen sulfate, triethylamine phosphate, triethylamine hydrogen phosphate, trimethylamine hydrohalide, trimethylamine sulfate, trimethylamine hydrogen sulfate, trimethylamine phosphate, trimethylamine hydrogen phosphate, diisopropyl Ethylamine hydrohalide, diisopropylethylamine sulfate, diisopropylethylamine sulfate, diisopropylethylamine phosphate, pyridine hydrohalide, pyridine sulfate, pyridine hydrogen sulfate, Pyridine phosphate, hydrogen pyridine phosphate, N-methylmorpholine hydrohalide, N-methylmorpholine sulfate, N-methylmorpholine hydrogen sulfate, N-methylmorpholine phosphate, N- Methylmorpholine hydrogen phosphate, N-methylpiperidine hydrohalide, N-methylpiperidine sulfate, N-methylpiperidine hydrogen sulfate, N-methylpiperidine phosphate, N-methyl Piperidine hydrogen phosphate, N-methyltetrahydropyrrole hydrohalide, N-methyltetrahydropyrrole sulfate, N-methyltetrahydropyrrole hydrogen sulfate, N-methyltetrahydropyrrole phosphate, N-methyltetrahydropyridine Hydrogen phosphate, tributyltin chloride, anhydrous zinc chloride, zinc chloride dihydrate, anhydrous titanium tetrachloride, etc., more preferably triethylamine hydrogen chloride, triethylamine sulfate, triethylamine sulfate One of hydrogen salt, pyridine hydrochloride and anhydrous zinc chloride, or any combination thereof;

In the present invention, the temperature range of the tetrazolium ring-forming reaction in step (1) is 70-180 ° C, and more preferably 100-140 ° C.

In some specific embodiments of the present invention, the brine described in step (2) is selected from one or any combination of sodium chloride aqueous solution, magnesium chloride aqueous solution, potassium chloride aqueous solution, calcium chloride aqueous solution, sodium sulfate aqueous solution. More preferably, it is a saturated aqueous sodium chloride solution or a 10-20% sodium chloride aqueous solution by mass.

In some specific embodiments of the present invention, the first extraction solvent described in step (2) is a solvent that can dissolve the valsartan methyl ester intermediate and is immiscible with water, and is preferably selected from toluene, xylene, and xylene. One of methyl chloride, methyl tert-butyl ether, isopropyl ether, n-butyl ether, anisole, phenyl ether, n-hexyl ether, n-heptyl ether, or any combination thereof, more preferably toluene, xylene, methyl ether T-butyl ether, anisole or n-butyl ether.

In some specific embodiments of the present invention, the heating temperature during the heating extraction in step (2) ranges from 35 to 140 ° C, preferably from 45 to 100 ° C.

In some specific embodiments of the present invention, the quencher is selected from one or a combination of nitrite, hypochlorite or hypobromite, and is preferably selected from sodium nitrite, nitrite One or any combination of potassium, sodium hypochlorite, sodium hypobromite, calcium hypobromite, calcium hypochlorite, etc., is preferably selected from sodium nitrite or sodium hypochlorite.

In some specific embodiments of the present invention, when the azide in the aqueous layer is quenched, the acid used to form the acidic condition is an inorganic strong acid, preferably one of hydrochloric acid and sulfuric acid or a combination thereof; and the pH is adjusted after the acid is added The value range is 0-5, preferably 1-3.

In some specific embodiments of the present invention, when the azide in the water layer is quenched in step (2), the temperature range of the water layer is -5-40 ° C, preferably 5-20 ° C.

In some specific embodiments of the present invention, the alkali solution described in step (3) is one of a hydroxide aqueous solution, a carbonate aqueous solution, or a combination thereof, and more preferably a 30% sodium hydroxide aqueous solution by mass. Or 30% potassium hydroxide aqueous solution by mass.

In some specific embodiments of the present invention, after adding the alkali solution in step (3), the hydrolysis reaction is performed with stirring. The temperature of the hydrolysis reaction ranges from -10 to 40 ° C, preferably from 0 to 20 ° C; the reaction time ranges from 5 to 40 hours. It is preferably 15-25 hours.

In some specific embodiments of the present invention, the step of adjusting the pH of the aqueous layer to acidic with a second acid described in step (3), the second acid used is an inorganic strong acid, preferably one of hydrochloric acid and sulfuric acid Or a combination thereof; the pH is adjusted in the range of 0.5-6, preferably 1-3 after the acid is added.

In some specific embodiments of the present invention, the second extraction solvent used in step (3) is a solvent that can be separated from the water layer, and is preferably ethyl acetate or methyl tert-butyl ether.

In some specific embodiments of the present invention, the new solvent in step (3) is a single solvent that can dissolve valsartan and a mixture of multiple solvents, and is preferably selected from ethyl acetate, acetone, ethanol, and isopropanol. Or a mixed solvent of ethyl acetate and dichloromethane; more preferably, in a mixed solvent of ethyl acetate and dichloromethane, the volume ratio of ethyl acetate to dichloromethane is 1: 3 to 3: 1.

In some specific embodiments of the present invention, the desiccant described in step (3) is selected from one or a combination of anhydrous chloride metal salts, anhydrous metal sulfate salts, and preferably selected from anhydrous magnesium sulfate. Or anhydrous sodium sulfate.

In some specific embodiments of the present invention, the crystallization solvent described in step (4) is a single solvent or a mixed solvent of multiple solvents capable of dissolving valsartan, and is preferably ethyl acetate or ethyl acetate and dichloromethane. More preferably, in a mixed solvent of ethyl acetate and dichloromethane, the volume ratio of ethyl acetate to dichloromethane is 1: 3 to 3: 1.

The method for synthesizing valsartan provided by the present invention, by separating the valsartan methyl ester intermediate before quenching the azide, avoids the highly toxic N-substance produced during the azide quenching process from the source of the process. The possibility that impurities such as nitrodimethylamine (NDMA), valsartan impurity K, and valsartan N-chloride are carried into the valsartan methyl ester intermediate, and then into the valsartan drug substance. To ensure the safety of valsartan medication.

**detailed description**

In order to make the objectives, technical solutions, and advantages of the present invention clearer, the following examples are used to further describe the present invention in detail. Obviously, the described embodiments are only a part of the embodiments of the present invention, but not all the embodiments. Based on the embodiments of the present invention, all other embodiments obtained by a person of ordinary skill in the art without creative efforts shall fall within the protection scope of the present invention.

Synthesis Example of Valsartan

In the following examples and comparative examples of the present invention, GC-MS method is used to detect N-nitrosodimethylamine (NDMA) in the finished valsartan, and LC-MS method is used to evaluate the finished valsartan. Valsartan impurity K and valsartan N-chloride in the detection; first, GC-MS (gas chromatography-mass spectrometry) and LC-MS (liquid phase liquid chromatography) used in the following examples and comparative examples of the present invention Chromatography-mass spectrometry) test method will be described.

1. GC-MS chromatographic conditions and detection methods:

Instrument: ThermoFischer Gas Chromatography Single Quadrupole Mass Spectrometer (Trace 1300 & ISQLT)

Column: DB-1701, 60m × 0.32mm, 1.8μm (14% cyanopropylphenyl-86% dimethyl polysiloxane copolymer)

Carrier gas: Helium

Linear speed: 1.0mL / min

Inlet temperature: 180 ℃

Injection volume: 2.0 μL

Split ratio: 25: 1

Heating program:

The initial temperature is 60 ° C, hold for 2min, then increase the temperature to 240 ° C at a rate of 15 ° C / min, and hold for 5min.

Ion source mode: EI, positive ion

Ion source: 250 ° C

Quadrupole temperature: 160 ℃

Relative voltage: 200V

Scanning mode: single ion extraction mode (SIM)

SIM ion current: m / z 74.0

Diluent: DMSO

Blank solution: same as diluent;

Standard solution preparation of N-nitrosodimethylamine (NDMA) reference substance: Weigh an appropriate amount of N-nitrosodimethylamine (NDMA) reference substance and dilute it to the NDMA concentration with the dilution solution: 0.2, 0.8, 3.2, 6.4, 20 micrograms / mL, shake until completely dissolved and ready to use.

Detection of N-nitrosodimethylamine (NDMA) content in the test sample (the finished valsartan prepared in the following examples and comparative examples):

Weigh 400 mg of the sample to be tested, accurately weigh it in a 20 mL headspace bottle, and then accurately remove 2 mL of the diluent, shake to dissolve, mix well, and use it as the test solution. The above GC-MS method was used to test the test solution and the NDMA standard solution of different concentrations, and the standard curve method was used to calculate the NDMA content in the test sample;

2. LC-MS chromatographic conditions and detection methods:

Instrument: Agilent LC-QTOF high-precision liquid chromatography-mass spectrometer (Agilent 6120 & 6545)

Column: Waters Symmetry C8, 250 × 4.6mm; 5μm

Mobile phase A: 0.1% formic acid in water

Mobile phase B: acetonitrile

Column temperature: 35 ° C

Injection volume: 10 μL

Detection wavelength: 230nm (200-400nm full scan of DAD spectrum)

Gradient table:

| 时间(min) | 流动相 A(%V/V) | 流动相 B(%V/V) | 流速（mL/min） |
|---|---|---|---|
| 0 | 50 | 50 | 1.2 |
| 4 | 50 | 50 | 1.2 |
| 16 | 20 | 80 | 1.2 |
| 24 | 20 | 80 | 1.2 |
| 26 | 50 | 50 | 1.2 |
| 35 | 50 | 50 | 1.2 |

Ion source: ESI ion source

Mass detector parameters:

| 质谱检测器参数 | | | |
|---|---|---|---|
| 干燥气体流速 | 6 L/min | $MS_1$ 扫描模式 | Full scan |
| 干燥气体温度 | 325 ℃ | $MS_1$ 扫描时间 | 5~40 min |
| 雾化气体压力 | 35 psi | $MS_1$ 扫描范围 | *m/z* 100-1700 |
| 毛细管电压 | +3500 V | 鞘气流速 | 12 L/min |
| 离子模式 | ESI 正离子 | 鞘气温度 | 350℃ |
| 碎片电压 | 90 V | 目标离子 1 | *m/z* 381.167（缬沙坦杂质 K） |
| 目标离子 2 | *m/z* 386.138（缬沙坦 N-氯代物） | 离子抽提误差 | 10 ppm |

Standard solution preparation of Valsartan impurity K reference substance: Weigh an appropriate amount of Valsartan impurity K reference substance and dilute it with a diluent (0.1% formic acid aqueous solution: acetonitrile = 2: 1 (v / v)) to a concentration of: 0.2, 0.8, 3.2, 6.4, 20 μg / mL, shake until completely dissolved, and then use.

Valsartan N-chloride reference standard solution preparation: Weigh an appropriate amount of valsartan N-chloride reference standard and dilute it with a dilution solution (0.1% formic acid aqueous solution: acetonitrile = 2: 1) to a concentration of 0.2, 0.8, 3.2, 6.4, 20 micrograms / mL, shake until completely dissolved, and then use.

Detection of the content of valsartan impurity K in the test sample: Weigh 400 mg of the test sample, accurately weigh it in a 20 mL headspace bottle, and accurately transfer 2 mL of the dilution solution (0.1% formic acid aqueous solution: acetonitrile = 2: 1) Shake to dissolve and mix as the test solution. The above-mentioned LC-MS method was used to test the test solution and different concentrations of valsartan impurity K standard solutions, and the standard curve method was used to calculate the content of valsartan impurity K.

Valsartan N-chloride content in the test sample: Weigh 400mg of the test sample, accurately weigh it in a 20mL headspace bottle, and accurately transfer 2mL of the dilution solution (0.1% formic acid aqueous solution: acetonitrile = 2: 1) , Shake to dissolve, mix well, as a test solution. The above LC-MS method was used to test the test solution and different concentrations of valsartan N-chloride standard solution, and the standard curve method was used to calculate the content of valsartan N-chloride.

Example 1

Synthesis of valsartan

Add 100 mL of N, N-dimethylformamide (DMF) solution of valsartan cyanide intermediate (containing 70 g of valsartan cyanide intermediate) to the reaction flask, followed by 36 g of anhydrous zinc chloride And 25g of sodium azide, the temperature was raised to 125-135 ° C, and the reaction was stirred for 28 hours. After the reaction was completed, the temperature was lowered to 45-48 ° C, and then 500 mL of methyl tert-butyl ether and 400 mL of 20% (w / w) chlorine were added. The aqueous sodium chloride solution was stirred at 45-48 ° C for 1 hour. The stirring was stopped. The layers were separated and the aqueous layer was separated. The organic layer was added to 200 mL of saturated saline at 45-48 ° C and continued to be stirred for 2 hours. The aqueous layer was separated. The layers were further washed with 200 mL of saturated saline at the same temperature and stirred for 2.5 hours, and the organic layer was separated. The separated water layers were combined 3 times for the subsequent azide quenching process.

Transfer the last separated organic layer to another reaction bottle, cool to 10-15 ° C, then add 55mL of 30% (w / w) NaOH aqueous solution and 105mL of water, stir the reaction for 15-20 hours, and let it stand for 5 minutes. Based on the tert-butyl ether layer, the temperature of the water layer was further lowered to 0 to 10 ° C, and a 4 mol / L hydrochloric acid solution was added dropwise to a pH of 1 to 2, and then 600 mL of ethyl acetate was added, and the water layer was separated after stirring for 30 minutes. Then, 350 mL of ethyl acetate was distilled off under reduced pressure at 40 ° C. If the water content was higher than 0.4%, 200 mL of fresh ethyl acetate (water content less than 0.01% (w / w)) was added, and then at 40 ° C. 200 mL of ethyl acetate was distilled off under reduced pressure until the moisture content was less than or equal to 0.4 (w / w)% (final moisture content was 0.35% (w / w)), the temperature was lowered to 0-10 ° C, and crystallization was performed for 10 hours. The crude valsartan is obtained, and it is directly put into the crystallization process of the finished valsartan without drying.

Put the crude valsartan obtained in the previous step into the reaction flask, then add 400 mL of ethyl acetate, heat to 35-40 ° C and stir until dissolved and clear, then slowly cool to 10-20 ° C, continue crystallization for 2 hours, stop stirring, Filtration followed by washing with 30 mL of ethyl acetate at 10-15 ° C, and drying yielded 63.g of the finished valsartan with a yield of 85%.

GC-MS method was used to detect N-nitrosodimethylamine (NDMA) in valsartan finished products, LC-MS method was used to detect valsartan impurity K and valsartan N-chlorine in valsartan finished products Substitutes were detected, and the detection results were not detected (the impurity concentration was lower than the sensitivity of the detection method, and no peak appeared).

Quenching of azides

Transfer the combined aqueous layer to the reaction flask, add 13g of sodium nitrite, lower the temperature to 15 ° C, and then slowly add 90mL of a 3mol / L dilute hydrochloric acid solution, and continue stirring for 30 minutes to quench the azide; After further concentration and desalination, the wastewater can be discharged into a low-concentration wastewater tank for further processing.

Example 2

Synthesis of valsartan

Add 100 mL of N, N-dimethylformamide (DMF) solution of valsartan cyanide intermediate (containing 60 g of valsartan cyanide intermediate) to the reaction flask, followed by 34 g of anhydrous zinc chloride And 29 g of potassium azide, the temperature was raised to 135 to 140 ° C, and the reaction was stirred for 20 hours. After the reaction was completed, the temperature was lowered to 90 to 100 ° C, and then 600 mL of n-butyl ether and 460 mL of 20% (w / w) sodium chloride were added. The aqueous solution was stirred at 90 to 100 ° C for 3 hours. The stirring was stopped, and the layers were separated. The aqueous layer was separated. The organic layer was added to 200 mL of saturated saline at 90 to 100 ° C and continued to be stirred for 2 hours. The aqueous layer was separated and the organic layer was separated. At the same temperature, washing and stirring were continued with 200 mL of saturated saline for 2 hours, and the organic layer was separated. The separated water layers were combined 3 times for the subsequent azide quenching process.

Transfer the last separated organic layer to another reaction flask, cool to 10-15 ° C, then add 50mL of 30% (w / w) NaOH aqueous solution and 100mL of water, stir the reaction for 15-20 hours, and let it stand for 10 minutes. In the butyl ether layer, the temperature of the water layer was further lowered to 0 to 10 ° C. A 4 mol / L sulfuric acid solution was added dropwise to a pH of 1 to 3, and then 550 mL of ethyl acetate was added. After stirring for 30 minutes, the water layer was separated, and then added. 50g of anhydrous magnesium sulfate was stirred for 2 hours until the moisture content was 0.2%, filtered, and magnesium sulfate was removed. Then, 340 mL of ethyl acetate was distilled off under reduced pressure at 40 ° C, and the temperature was lowered to 0 to 5 ° C. The crystals were crystallized for 8 hours and filtered to obtain valerium. The crude sartan is directly put into the crystallization process of the finished valsartan without drying.

Put the crude valsartan obtained in the previous step into a reaction flask, then add 300 mL of ethyl acetate, heat to 40 to 42 ° C and stir until dissolution and clarification, then slowly lower the temperature to 0 to 5 ° C, continue crystallization for 2 hours, and stop stirring. Filtration followed by washing with 30 mL of ethyl acetate at 0 to 2 ° C, and drying yielded 55.3 g of a finished valsartan with a yield of 86%.

GC-MS method was used to detect N-nitrosodimethylamine (NDMA) in valsartan finished products, LC-MS method was used to detect valsartan impurity K and valsartan N-chlorine in valsartan finished products The surrogates were tested, and the test results were not detected.

Quenching of azides

Transfer the combined aqueous layer to the reaction flask, add 12g sodium hypochlorite, adjust the temperature to 20 ° C, and then slowly drop 120mL 2mol / L dilute sulfuric acid solution, and continue stirring for 30 minutes to quench the azide; After further concentration and desalination, the wastewater can be discharged into a low-concentration wastewater tank for further processing.

Example 3

Synthesis of valsartan

Add 130 mL of N, N-dimethylformamide (DMF) solution of valsartan cyanide intermediate (containing valsartan cyanide intermediate 80g) to the reaction flask, followed by 45g of anhydrous zinc chloride And 30g of sodium azide, the temperature was raised to 130-135 ° C, and the reaction was stirred for 24 hours. After the reaction was completed, the temperature was lowered to 90-100 ° C, and then 440mL of toluene and 440mL of a 20% (w / w) sodium chloride aqueous solution were added. Stir at ~ 100 ° C for 2 hours, stop stirring, stand still and separate, separate the aqueous layer, add 220mL of saturated saline at 90 ~ 100 ° C, continue to wash and stir for 2 hours, separate the aqueous layer, and the organic layer again in the same The mixture was washed and stirred with 220 mL of saturated saline at a temperature for 2 hours, and the organic layer was separated. The separated water layers were combined 3 times for the subsequent azide quenching process.

Transfer the last separated organic layer to another reaction flask, cool to 10-15 ° C, then add 65mL 30% NaOH aqueous solution and 140mL water, stir the reaction for 15-20 hours, leave the toluene layer and separate the aqueous layer. The temperature was further lowered to 0 to 10 ° C, 6 mol / L hydrochloric acid solution was added dropwise to a pH of 1 to 2, then 700 mL of ethyl acetate was added, and the aqueous layer was separated after stirring for 30 minutes, and then distilled off under reduced pressure at 40 ° C. 400mL of ethyl acetate, if the moisture content is higher than 0.5%, continue to add 200mL of fresh ethyl acetate (water content is less than 0.01%), and then distill off 200mL ethyl acetate under reduced pressure at 40 ° C until the water content is lower than Or equal to 0.5% (final moisture content is 0.28%), reduce the temperature to 0-10 ° C, crystallize for 10 hours, filter to obtain the crude valsartan, and directly put it into the crystallization process of the finished valsartan without drying.

Put the crude valsartan obtained in the previous step into the reaction flask, then add 540 mL of ethyl acetate, stir to 40 to 45 ° C until the solution is clear, then slowly cool to -5 to 5 ° C, continue crystallization for 2 hours, and stop stirring , Filtered, and then washed with 50 mL of ethyl acetate at 0 ~ 2 ° C, dried to obtain 75.6 g of valsartan finished product, yield 87%.

GC-MS method was used to detect N-nitrosodimethylamine (NDMA) in valsartan finished products, LC-MS method was used to detect valsartan impurity K and valsartan N-chlorine in valsartan finished products The surrogates were tested, and the test results were not detected.

Quenching of azides

Transfer the combined aqueous layer to the reaction flask, add 15g of sodium nitrite, lower the temperature to 10 ° C, and then slowly drop 120mL of a 3mol / L dilute hydrochloric acid solution, and continue stirring for 30 minutes to quench the azide; After further concentration and desalination, the wastewater can be discharged into a low-concentration wastewater tank for further processing.

Example 4

Synthesis of valsartan

Add 250 mL of N, N-dimethylformamide (DMF) solution of valsartan cyanide intermediate (containing valsartan cyanide intermediate 160g) to the reaction flask, followed by 92g of anhydrous zinc chloride And 106 g of trimethylsilazide (TMSN $_3$ ), the temperature was raised to 130 to 135 ° C and the reaction was stirred for 28 hours. After the reaction was completed, the temperature was lowered to 90 to 100 ° C, and then 800 mL of xylene and 850 mL of 20% (w / w) were added. ) Sodium chloride aqueous solution, stir at 90-100 ° C for 2 hours, stop stirring, separate the layers, separate the aqueous layer, add 450mL of saturated saline at 90-100 ° C, continue to wash and stir for 3 hours, and separate the aqueous layer The organic layer was further washed and stirred with 450 mL of saturated saline at the same temperature for 3 hours, and the organic layer was separated. The separated water layers were combined 3 times for the subsequent azide quenching process.

Transfer the last separated organic layer to another reaction flask, cool to 10-15 ° C, then add 130mL of 30% (w / w) NaOH aqueous solution and 280mL of water, stir the reaction for 14-18 hours, and let it stand for 2 minutes In the toluene layer, the temperature of the aqueous layer was further lowered to -5 to 0 ° C. A 6 mol / L hydrochloric acid solution was added dropwise to a pH of 1.0 to 2.0. Then, 1500 mL of ethyl acetate was added, and the aqueous layer was separated after stirring for 30 minutes. 900 mL of ethyl acetate was distilled off under reduced pressure at 200 ° C. If the moisture content was higher than 0.3%, 200 mL of fresh ethyl acetate was added (water content below 0.01%), and then 200 mL of ethyl acetate was distilled off under reduced pressure at 40 ° C. Until the moisture content is less than 0.3% (final moisture content is 0.25%), the temperature is lowered to -5 to 0 ° C, and crystallization is performed for 12 hours, and the crude valsartan is filtered, and the valsartan product is directly crystallized without drying.

Put the crude valsartan obtained in the previous step into a reaction flask, then add 1000 mL of ethyl acetate, stir to 40 to 45 ° C until the solution is clear, then slowly lower the temperature to 0 to 3 ° C, continue crystallization for 3 hours, and stop stirring. Filtration, followed by washing with 80 mL of ethyl acetate at 0 to 2 ° C, and drying to obtain 150.8 g of the finished valsartan, with a yield of 88%.

GC-MS method was used to detect N-nitrosodimethylamine (NDMA) in valsartan finished products, LC-MS method was used to detect valsartan impurity K and valsartan N-chlorine in valsartan finished products The surrogates were tested, and the test results were not detected.

Quenching of azides

Transfer the combined aqueous layer to the reaction flask, add 30g of sodium nitrite, lower the temperature to 15 ° C, then slowly add 200mL of 3mol / L dilute sulfuric acid solution, and continue stirring for 30 minutes to quench the azide; After further concentration and desalination, the wastewater can be discharged into a low-concentration wastewater tank for further processing.

Example 5

Synthesis of valsartan

Add 130 mL of N, N-dimethylformamide (DMF) solution of valsartan cyanide intermediate (containing valsartan cyanide intermediate 80g) to the reaction flask, followed by 48 g of triethylamine hydrochloride The salt and 30 g of sodium azide were heated to 120 to 125 ° C and stirred for 28 hours. After the reaction was completed, the temperature was lowered to 90 to 100 ° C. Then 450 mL of toluene and 200 mL of water were added, and the mixture was stirred at 90 ° C for 2 hours to stop stirring. Allow the layers to separate and separate the aqueous layer. Add 260 mL of saturated saline at 90 to 100 ° C and continue to wash and stir for 2 hours. Separate the aqueous layer and continue to wash and stir the organic layer with 260 mL of saturated saline at the same temperature. After 2 hours, the organic layer was separated. The separated water layers were combined 3 times for the subsequent azide quenching process.

Transfer the last separated organic layer to another reaction flask, cool to 5-10 ° C, then add 65mL of 30% NaOH aqueous solution and 140mL of water, stir the reaction for 20-25 hours, leave the toluene layer separated, and separate the aqueous layer The temperature was further lowered to 0 to 10 ° C, and a 6mol / L hydrochloric acid solution was added dropwise to a pH of 1 to 3, and then 700 mL of ethyl acetate was added. After stirring for 30 minutes, the aqueous layer was separated, and then 400 mL was distilled off under reduced pressure at 40 ° C. Ethyl acetate, if the water content is higher than 0.5%, continue to add 200mL of fresh ethyl acetate (water content is less than 0.01%), and then distill off 200mL of ethyl acetate under reduced pressure at 40 ° C until the water content is lower than or It is equal to 0.5% (final moisture content is 0.25%), the temperature is lowered to 0 to 10 ° C., and crystallization is performed for 10 hours. The crude valsartan is filtered, and the valsartan product is directly crystallized without drying.

Put the crude valsartan obtained in the previous step into the reaction flask, then add 700 mL of ethyl acetate-dichloromethane mixed solution (volume ratio of 2: 1), stir to 40-45 ° C until dissolved and clarify, and then slowly cool down The temperature was maintained at -5 to 5 ° C, and the crystallization was continued for 2 hours. The stirring was stopped, and then filtered, and then washed with 50 mL of ethyl acetate at 0 to 2 ° C. The dried valsartan product was 69.4 g in a yield of 81%.

GC-MS method was used to detect N-nitrosodimethylamine (NDMA) in valsartan finished products, LC-MS method was used to detect valsartan impurity K and valsartan N-chlorine in valsartan finished products The surrogates were tested, and the test results were not detected.

Quenching of azides

Transfer the combined water layer to the reaction flask, add 20g potassium nitrite, cool down to 10 ℃, and then slowly add 120mL 3mol / L dilute hydrochloric acid solution, and continue stirring for 30 minutes to quench the azide; After further concentration and desalination, the wastewater can be discharged into a low-concentration wastewater tank for further processing.

Example 6

Synthesis of valsartan

Add 130 mL of N, N-dimethylformamide (DMF) solution of valsartan cyanide intermediate (containing valsartan cyanide intermediate 80g) to the reaction flask, followed by 42g of triethylamine sulfate And 50 g of trimethylsilazide (TMSN $_3$ ), and the reaction was stirred for 35 hours at 110 to 120 ° C. After the reaction was completed, the temperature was lowered to 90 to 100 ° C, and then 500 mL of toluene and 500 mL of a 20% aqueous sodium chloride solution were added. Stir at 90 ° C for 2 hours, stop stirring, separate the layers, separate the aqueous layer, add 250mL of saturated saline at 90-100 ° C, continue to wash and stir for 2 hours, separate the aqueous layer, and the organic layer at the same temperature again The mixture was further washed with 250 mL of saturated saline and stirred for 2 hours, and the organic layer was separated. The separated water layers were combined 3 times for the subsequent azide quenching process.

Transfer the last separated organic layer to another reaction flask, cool to 5-10 ° C, then add 60mL 30% NaOH aqueous solution and 120mL water, stir the reaction for 20-25 hours, leave the toluene layer separated, and separate the aqueous layer The temperature was further lowered to 0 to 10 ° C, and a 6 mol / L hydrochloric acid solution was added dropwise to a pH of 2 to 3, and then 700 mL of ethyl acetate was added. After stirring for 30 minutes, the aqueous layer was separated. After stirring for 30 minutes, the aqueous layer was separated. Add 80g of anhydrous sodium sulfate and stir for 2 hours until the moisture content is 0.18%, filter, remove the sodium sulfate, and then distill off 400 mL of ethyl acetate under reduced pressure at 40 ° C, reduce the temperature to 0-5 ° C, crystallize for 8 hours, and filter to obtain Crude valsartan, directly into the crystallization process of the finished valsartan without drying.

Put the crude valsartan obtained in the previous step into the reaction flask, then add 900 mL of ethyl acetate-dichloromethane mixed solution (volume ratio of 1: 1), stir to 40-45 ° C until dissolved and clarified, and then slowly cool down To -5 to 5 ° C, continue to crystallize for 2 hours, stop stirring, filter, and then wash with 100mL of ethyl acetate-dichloromethane mixed solution (volume ratio of 1: 1) at 0 to 2 ° C, and dry to obtain valsartan. The finished product was 62.6 g, and the yield was 73%.

GC-MS method was used to detect N-nitrosodimethylamine (NDMA) in valsartan finished products, LC-MS method was used to detect valsartan impurity K and valsartan N-chlorine in valsartan finished products The surrogates were tested, and the test results were not detected.

Quenching of azides

Transfer the combined aqueous layer to the reaction flask, add 13g of calcium hypochlorite, lower the temperature to 10 ℃, then slowly add 100mL of 3mol / L dilute sulfuric acid solution, and continue stirring for 30 minutes to quench the azide After further concentration and desalination, the wastewater can be discharged into a low-concentration wastewater tank for further processing.

Example 7

Synthesis of valsartan

Add 250 mL of N, N-dimethylformamide (DMF) solution of valsartan cyanide intermediate (containing 160 g of valsartan cyanide intermediate) to the reaction flask, followed by 130 g of triethylamine hydrogen sulfate Salt and 106 g of trimethylsilazide ($TMSN_3$), and the reaction was stirred at 130-135 ° C for 28 hours. After the reaction was completed, the temperature was lowered to 75-85 ° C, and then 800 mL of anisole and 500 mL of 10% chloride were added. Aqueous sodium solution was stirred at 75-85 ° C for 2 hours. The stirring was stopped. The layers were separated and the aqueous layer was separated. The organic layer was added to 450 mL of saturated saline at 75-85 ° C to continue washing and stirring for 3 hours. The aqueous layer and the organic layer were separated. At the same temperature, the mixture was further washed with 450 mL of saturated saline and stirred for 3 hours, and the organic layer was separated. The separated water layers were combined 3 times for the subsequent azide quenching process.

Transfer the last separated organic layer to another reaction flask, cool to 10-15 ° C, then add 130mL of 30% NaOH aqueous solution and 280mL of water, stir the reaction for 14-18 hours, and leave to separate the anisole layer. The temperature of the aqueous layer was further lowered to -5 to 0 ° C. A 6 mol / L hydrochloric acid solution was added dropwise to a pH of 1.5 to 2.5. Then 1500 mL of ethyl acetate was added. After stirring for 30 minutes, the aqueous layer was separated, and the pressure was reduced at 40 ° C. Evaporate all the ethyl acetate, then add 600 mL of acetone, dissolve it at 40 ° C and finally dissolve it at a final moisture content of 0.17%. Slowly reduce the temperature to 0-5 ° C and crystallize for 12 hours. Filter to obtain the crude valsartan. The crystallization process of the finished valsartan is introduced.

Put the crude valsartan obtained in the previous step into a reaction flask, then add 1000 mL of ethyl acetate, stir to 40 to 45 ° C until the solution is clear, then slowly lower the temperature to 0 to 3 ° C, continue crystallization for 3 hours, and stop stirring. Filtration, followed by washing with 80 mL of ethyl acetate at 0 to 2 ° C, and drying to obtain 140.6 g of the finished valsartan, with a yield of 82%.

GC-MS method was used to detect N-nitrosodimethylamine (NDMA) in valsartan finished products, LC-MS method was used to detect valsartan impurity K and valsartan N-chlorine in valsartan finished products The surrogates were tested, and the test results were not detected.

Quenching of azides

Transfer the combined aqueous layer to the reaction flask, add 30g of sodium nitrite, cool down to 15 ℃, then slowly add 180mL of 3mol / L dilute hydrochloric acid solution, continue stirring for 30 minutes, and then quench the azide After further concentration and desalination, the wastewater can be discharged into a low-concentration wastewater tank for further processing.

Example 8

Synthesis of valsartan

Add 130 mL of N, N-dimethylformamide (DMF) solution of valsartan cyanide intermediate (containing 80 g of valsartan cyanide intermediate) to the reaction flask, followed by 95 g of pyridine hydrochloride and 30g of sodium azide was heated to 130-140 ° C and stirred for 24 hours. After the reaction was completed, the temperature was lowered to 90-100 ° C. Then 440mL of toluene and 440mL of a 20% magnesium chloride aqueous solution were added. The mixture was stirred at 90 ° C for 2 hours and the stirring was stopped. , Let stand and separate the layers, separate the aqueous layer, add 300mL of saturated magnesium chloride aqueous solution at 90 ~ 100 ℃, continue washing and stir for 2 hours, separate the aqueous layer, and continue to wash the organic layer with 300mL of saturated magnesium chloride aqueous solution at the same temperature. After stirring for 2 hours, the organic layer was separated. The separated water layers were combined 3 times for the subsequent azide quenching process.

Transfer the last separated organic layer to another reaction flask, cool to 10-15 ° C, then add 65mL 30% NaOH aqueous solution and 140mL water, stir the reaction for 15-20 hours, leave the toluene layer and separate the aqueous layer. The temperature was further lowered to 0 to 10 ° C, 6 mol / L hydrochloric acid solution was added dropwise to a pH of 2 to 3, and then 700 mL of ethyl acetate was added. After stirring for 30 minutes, the aqueous layer was separated, and then the whole was distilled off under reduced pressure at 40 ° C. 500 mL of isopropyl alcohol was added, and the temperature was raised to 40 ° C to dissolve all, the final moisture content was 0.15%, the temperature was lowered to 0-10 ° C, and the crystals were crystallized for 10 hours. Crystallization of the finished product.

Put the crude valsartan obtained in the previous step into the reaction flask, then add 540 mL of ethyl acetate, stir to 40 to 45 ° C until the solution is clear, then slowly cool to -5 to 5 ° C, continue crystallization for 2 hours, and stop stirring , Filtered, then washed with 50 mL of ethyl acetate at 0 ~ 2 ° C, dried to obtain 80.0 g of valsartan finished product, yield 84%.

GC-MS method was used to detect N-nitrosodimethylamine (NDMA) in valsartan finished products, LC-MS method was used to detect valsartan impurity K and valsartan N-chlorine in valsartan finished products The surrogates were tested, and the test results were not detected.

Quenching of azides

Transfer the combined aqueous layer to the reaction flask, add 35g sodium hypobromite, cool down to 10 ℃, then slowly drop 120mL 3mol / L dilute hydrochloric acid solution, continue stirring for 30 minutes, you can quench the azide After further concentration and desalination, the wastewater can be discharged into a low-concentration wastewater tank for further processing.

Example 9

Synthesis of valsartan

Add 100 mL of N, N-dimethylformamide (DMF) solution of valsartan cyanide intermediate (containing 60 g of valsartan cyanide intermediate) to the reaction flask, followed by 34 g of anhydrous zinc chloride And 25g of sodium azide, the temperature was raised to 130-135 ° C, and the reaction was stirred for 28 hours. After the reaction was completed, the temperature was lowered to 60-70 ° C, and then 1000 mL of anisole and 460 mL of a 20% sodium sulfate aqueous solution were added at 60-70 ° C. Stir for 3 hours, stop stirring, stand still and separate layers, separate the aqueous layer, add 200 mL of saturated sodium sulfate aqueous solution at 60-70 ° C, continue to wash and stir for 2 hours, separate the aqueous layer, and use the organic layer at the same temperature again. 200 mL of a saturated sodium sulfate aqueous solution was continuously washed and stirred for 2 hours, and the organic layer was separated. The separated water layers were combined 3 times for the subsequent azide quenching process.

Transfer the last separated organic layer to another reaction flask, cool to 5-10 ° C, then add 60mL 30% NaOH aqueous solution and 100mL water, stir the reaction for 15-20 hours, and leave to separate the anisole layer. The temperature of the aqueous layer was further lowered to 0 to 10 ° C. A 6 mol / L hydrochloric acid solution was added dropwise to a pH of 1 to 3, followed by the addition of 550 mL of ethyl acetate. After stirring for 30 minutes, the aqueous layer was separated, followed by the addition of 50 g of anhydrous magnesium sulfate and stirred. 2 hours, until the moisture content is 0.21%, filter, remove magnesium sulfate, and then distill off 340 mL of ethyl acetate under reduced pressure at 40 ° C, lower the temperature to 0-5 ° C, crystallize for 8 hours, and filter to obtain crude valsartan without drying Directly put into the crystallization process of valsartan finished product.

Put the crude valsartan obtained in the previous step into a reaction flask, then add 300 mL of ethyl acetate, heat to 40 to 42 ° C and stir until dissolution and clarification, then slowly lower the temperature to 0 to 5 ° C, continue crystallization for 2 hours, and stop stirring. Filtration, followed by washing with 30 mL of ethyl acetate at 0 to 2 ° C, and drying yielded 57.2 g of a finished valsartan with a yield of 89%.

GC-MS method was used to detect N-nitrosodimethylamine (NDMA) in valsartan finished products, LC-MS method was used to detect valsartan impurity K and valsartan N-chlorine in valsartan finished products The surrogates were tested, and the test results were not detected.

Quenching of azides

Transfer the combined aqueous layer to the reaction flask, add 12g sodium hypochlorite, adjust the temperature to 20 ° C, and then slowly drop 120mL 2mol / L dilute sulfuric acid solution, and continue stirring for 30 minutes to quench the azide; After further concentration and desalination, the wastewater can be discharged into a low-concentration wastewater tank for further processing.

Example 10

Synthesis of valsartan

Add 130 mL of N, N-dimethylformamide (DMF) solution of valsartan cyanide intermediate (containing valsartan cyanide intermediate 80g) to the reaction flask, followed by 45g of anhydrous zinc chloride And 30 g of sodium azide, the temperature was raised to 130-140 ° C, and the reaction was stirred for 24 hours. After the reaction was completed, the temperature was lowered to 80-90 ° C, and then 500 mL of xylene and 440 mL of a 20% sodium chloride aqueous solution were added at 80-90 ° C. Stir for 2 hours, stop stirring, stand still and separate the layers, separate the aqueous layer, add 220mL of saturated saline at 80-90 ° C, continue to wash and stir for 2 hours, separate the aqueous layer, and use the organic layer at the same temperature with 220mL. The saturated brine was washed and stirred for 2 hours, and the organic layer was separated. The separated water layers were combined 3 times for the subsequent azide quenching process.

Transfer the last separated organic layer to another reaction flask, cool to 10-15 ° C, then add 65mL of 30% NaOH aqueous solution and 140mL of water, stir the reaction for 15-20 hours, leave the xylene layer to stand, remove the water The layer temperature was further lowered to 0 to 10 ° C, and a 6 mol / L hydrochloric acid solution was added dropwise to a pH of 1 to 2, and then 700 mL of ethyl acetate was added. After stirring for 30 minutes, the aqueous layer was separated, and then evaporated under reduced pressure at 40 ° C. 400mL of ethyl acetate, if the moisture content is higher than 0.5%, continue to add 200mL of fresh ethyl acetate (water content is less than 0.01%), and then distill off 200mL of ethyl acetate under reduced pressure at 40 ° C to a moisture content of 0.24 %, Cool down to 5-8 ° C, crystallize for 10 hours, filter to obtain the crude valsartan, and directly put it into the crystallization process of the finished valsartan without drying.

Put the crude valsartan obtained in the previous step into the reaction flask, then add 900 mL of ethyl acetate-dichloromethane mixed solution (volume ratio of 1: 3), stir to 40-45 ° C until dissolved and clarified, and then slowly cool down Continue to crystallize to 5-10 ° C for 2 hours, stop stirring, filter, and then wash with 90mL 5-8 ° C ethyl acetate-dichloromethane mixed solution (volume ratio of 1: 3) and dry to obtain the finished valsartan 71.1 g, yield 83%.

GC-MS method was used to detect N-nitrosodimethylamine (NDMA) in valsartan finished products, LC-MS method was used to detect valsartan impurity K and valsartan N-chlorine in valsartan finished products The surrogates were tested, and the test results were not detected.

Quenching of azides

Transfer the combined aqueous layer to the reaction flask, add 35g of calcium hypobromite, lower the temperature to 10 ℃, then slowly add 120mL of 3mol / L dilute hydrochloric acid solution, and continue stirring for 30 minutes to quench the azide After further concentration and desalination, the wastewater can be discharged into a low-concentration wastewater tank for further processing.

Example 11

Synthesis of valsartan

Add 130 mL of N, N-dimethylformamide (DMF) solution of valsartan cyanide intermediate (containing valsartan cyanide intermediate 80g) to the reaction flask, followed by 45g of anhydrous zinc chloride And 30 g of sodium azide, the temperature was raised to 130-140 ° C, and the reaction was stirred for 24 hours. After the reaction was completed, the temperature was lowered to 60-70 ° C, and then 600 mL of n-butyl ether and 440 mL of a 20% sodium chloride aqueous solution were added, 60-70. Stir for 3 hours at ℃, stop stirring, separate the layers, separate the aqueous layer, add 220mL of saturated saline at 60 ~ 70 ℃, continue to wash and stir for 2 hours, separate the aqueous layer, and the organic layer at the same temperature again The mixture was further washed with 220 mL of saturated saline and stirred for 2 hours, and the organic layer was separated. The separated water layers were combined 3 times for the subsequent azide quenching process.

Transfer the last separated organic layer to another reaction flask, cool to 5-10 ° C, then add 90 mL of 30% KOH aqueous solution and 150 mL of water, stir the reaction for 18 to 23 hours, and stand to remove the n-butyl ether layer. The temperature of the aqueous layer was further lowered to 0 to 10 ° C, and a 6 mol / L hydrochloric acid solution was added dropwise to a pH of 2 to 3, and then 700 mL of ethyl acetate was added. After stirring for 30 minutes, the aqueous layer was separated, and then 50 g of anhydrous magnesium sulfate was added. Stir for 2 hours until the moisture content is 0.2%, filter, remove magnesium sulfate, and then distill off 340 mL of ethyl acetate under reduced pressure at 40 ° C, lower the temperature to 0-10 ° C, crystallize for 10 hours, and filter to obtain the crude valsartan. Dry directly into the crystallization process of the finished valsartan.

Put the crude valsartan obtained in the previous step into the reaction flask, then add 540 mL of ethyl acetate, stir to 40 to 45 ° C until the solution is clear, then slowly cool to -5 to 5 ° C, continue crystallization for 2 hours, and stop stirring , Filtered, then washed with 50 mL of ethyl acetate at 0 ~ 2 ° C, and dried to obtain 65.1 g of

valsartan finished product, yield 76%.

GC-MS method was used to detect N-nitrosodimethylamine (NDMA) in valsartan finished products, LC-MS method was used to detect valsartan impurity K and valsartan N-chlorine in valsartan finished products The surrogates were tested, and the test results were not detected.

Quenching of azides

Transfer the combined aqueous layer to the reaction flask, add 15g of sodium nitrite, lower the temperature to 10 ° C, and then slowly drop 120mL of a 3mol / L dilute hydrochloric acid solution, and continue stirring for 30 minutes to quench the azide; After further concentration and desalination, the wastewater can be discharged into a low-concentration wastewater tank for further processing.

Example 12

Synthesis of valsartan

Add 130 mL of N, N-dimethylformamide (DMF) solution of valsartan cyanide intermediate (containing valsartan cyanide intermediate 80g) to the reaction flask, followed by 45g of anhydrous zinc chloride And 30g of sodium azide, the temperature was raised to 130-135 ° C, and the reaction was stirred for 22 hours. After the reaction was completed, the temperature was lowered to 75-80 ° C, and then 500 mL of toluene and 400 mL of a 20% sodium chloride aqueous solution were added and stirred at 75-80 ° C After 2 hours, stop stirring and let stand. The aqueous layer was separated. The organic layer was added to 200 mL of saturated saline at 75 to 80 ° C and washed and stirred for another 2 hours. The aqueous layer was separated and the organic layer was re-used at 200 mL with the same temperature. The saturated saline solution was continuously washed and stirred for 2 hours, and the organic layer was separated. The separated water layers were combined 3 times for the subsequent azide quenching process.

Transfer the last separated organic layer to another reaction flask, cool to 10-15 ° C, then add 65mL 30% NaOH aqueous solution and 140mL water, stir the reaction for 15-20 hours, leave the toluene layer and separate the aqueous layer. The temperature was further lowered to 0 to 10 ° C, 6 mol / L hydrochloric acid solution was added dropwise to a pH of 1 to 2, then 700 mL of ethyl acetate was added, and the aqueous layer was separated after stirring for 30 minutes, and then the whole was distilled off under reduced pressure at 40 ° C. Ethyl acetate, followed by the addition of 400 mL of isopropanol, heated to 40 ° C and dissolved (final moisture content is 0.21%), cooled to 0-10 ° C, crystallized for 10 hours, filtered to obtain crude valsartan, directly put without drying Crystallization of finished valsartan.

Put the crude valsartan obtained in the previous step into the reaction flask, then add 540 mL of ethyl acetate, stir to 40 to 45 ° C until the solution is clear, then slowly cool to -5 to 5 ° C, continue crystallization for 2 hours, and stop stirring , Filtered, and then washed with 50 mL of ethyl acetate at 0 ~ 2 ° C, and dried to obtain 70.3 g of valsartan finished product, yield 82%.

GC-MS method was used to detect N-nitrosodimethylamine (NDMA) in valsartan finished products, LC-MS method was used to detect valsartan impurity K and valsartan N-chlorine in valsartan finished products The surrogates were tested, and the test results were not detected.

Quenching of azides

Transfer the combined aqueous layer to the reaction flask, add 15g of sodium nitrite, lower the temperature to 10 ° C, and then slowly drop 120mL of a 3mol / L dilute hydrochloric acid solution, and continue stirring for 30 minutes to quench the azide; After further concentration and desalination, the wastewater can be discharged into a low-concentration wastewater tank for further processing.

Comparative Example 1

Add 130 mL of N, N-dimethylformamide (DMF) solution of valsartan cyanide intermediate (containing valsartan cyanide intermediate 80g) to the reaction flask, followed by 45g of anhydrous zinc chloride And 30 g of sodium azide, the temperature was raised to 130 to 135 ° C, and the reaction was stirred for 24 hours. After the reaction was completed, the temperature was lowered to 30 to 50 ° C, and then 50 mL of DMF, 3000 mL of methyl tert-butyl ether and 200 mL of water were added, 30 to 50 Stir at ℃ for 1 hour, cool to 0 ~ 10 ℃, then add 12g of sodium nitrite, stir for 30min, and slowly add 110mL 6mol / L dilute hydrochloric acid solution to the solution pH 1 ~ 2 while stirring at 0 ~ 10 ℃. Place and separate the organic layer.

The separated organic layer was transferred to another reaction flask, cooled to 10 to 15 ° C, and then 65 mL of 30% NaOH aqueous solution and 140 mL of water were added, and the reaction was stirred for 15 to 20 hours. The toluene layer was left to stand and the temperature of the water layer was further increased. Reduce the temperature to 0-10 ° C, dropwise add a 6mol / L hydrochloric acid solution to a pH of 1-2, then add 700mL of ethyl acetate, stir for 30 minutes, separate the aqueous layer, and then evaporate 400mL of ethyl acetate under reduced pressure at 40 ° C. For esters, if the moisture content is higher than 0.5%, continue to add 200 mL of fresh ethyl acetate (water content is less than 0.01%), and then distill off 200 mL of ethyl acetate under reduced pressure at 40 ° C until the moisture content is less than or equal to 0.5 % (Final moisture content is 0.28%), cooled to 0-10 ° C, crystallized for 10 hours, filtered to obtain the crude valsartan, and directly put into the crystallization process of the finished valsartan without drying.

Put the crude valsartan obtained in the previous step into the reaction flask, then add 540 mL of ethyl acetate, stir to 40 to 45 ° C until the solution is clear, then slowly cool to -5 to 5 ° C, continue crystallization for 2 hours, and stop stirring , Filtered, and then washed with 50 mL of ethyl acetate at 0 ~ 2 ° C, and dried to obtain 73.7 g of valsartan finished product, yield 86%.

GC-MS method was used to detect N-nitrosodimethylamine (NDMA) in valsartan finished products, LC-MS method was used to detect valsartan impurity K and valsartan N-chlorine in valsartan finished products Substitutes were tested; the content of each impurity was calculated using the standard curve method; the test results showed that the N-nitrosodimethylamine (NDMA) content was 22.6 ppm, the valsartan impurity K content was 47.5 ppm, and the valsartan N-chloride was not Check out.

Comparative Example 2

Add 100 mL of N, N-dimethylformamide (DMF) solution of valsartan cyanide intermediate (containing 60 g of valsartan cyanide intermediate) to the reaction flask, followed by 34 g of anhydrous zinc chloride And 25g of sodium azide, the temperature was raised to 130-135 ° C, and the reaction was stirred for 28 hours. After the reaction was completed, the temperature was lowered to 30-50 ° C, and then 40 mL of DMF, 2400 mL of methyl tert-butyl ether and 150 mL of water were added, and 30-50 Stir for 1 hour at ℃, cool to 0 ~ 10 ℃, then add 16g of sodium hypochlorite and stir for 30min, and slowly add 100mL 6mol / L dilute sulfuric acid solution to the solution pH 1 ~ 2 while stirring at 0 ~ 10 ℃. Separate the organic layer.

The separated organic layer was transferred to another reaction flask, cooled to 5-10 ° C, then 60 mL of 30% NaOH aqueous solution and 100 mL of water were added, and the reaction was stirred for 15-20 hours. The anisole layer was separated and the water layer was left to stand. The temperature was further lowered to 0 to 10 ° C, 6 mol / L hydrochloric acid solution was added dropwise to a pH of 1 to 3, and then 550 mL of ethyl acetate was added. After stirring for 30 minutes, the aqueous layer was separated, and then 50 g of anhydrous magnesium sulfate was added and stirred for 2 hours. , To a moisture content of 0.21%, filter, remove magnesium sulfate, and then distill off 340 mL of ethyl acetate under reduced pressure at 40 ° C, lower the temperature to 0-5 ° C, crystallize for 8 hours, filter to obtain the crude valsartan, and directly input without drying Crystallization of finished valsartan.

Put the crude valsartan obtained in the previous step into a reaction flask, then add 180 mL of ethyl acetate, heat to 40 to 42 ° C and stir until the solution is clear, then slowly lower the temperature to 0 to 5 ° C, continue crystallization for 2 hours, and stop stirring. Filtration followed by washing with 30 mL of ethyl acetate at 0 to 2 ° C, and drying yielded 56.6 g of a finished valsartan, with a yield of 88%.

GC-MS method was used to detect N-nitrosodimethylamine (NDMA) in valsartan finished products, LC-MS method was used to detect valsartan impurity K and valsartan N-chlorine in valsartan finished products Substitutes were tested; the content of each impurity was calculated using the standard curve method; the test results showed that N-nitrosodimethylamine (NDMA) and valsartan impurity K were not detected, and the content of valsartan N-chloride was 28.3 ppm.

The above only describes the preferred embodiments of the present invention in detail, and the present invention is not limited to the above embodiments, and any changes and modifications to the present invention belong to the protection scope of the present invention.

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| CN102010381A * | 2009-09-05 | 2011-04-13 | 山东新时代药业有限公司 | Improved preparation method of valsartan |
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| CN102911128A * | 2012-09-25 | 2013-02-06 | 苏州天绿生物制药有限公司 | Synthetic method of valsartan |
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* Cited by examiner, † Cited by third party

## Non-Patent Citations (2)

| Title |
|---|
| See also references of EP3822259A4 |
| XU MENG: "Research on the Synthesis of High Optical Purity Valsartan", CHINESE MASTER'S THESES FULL-TEXT DATABASE, 1 April 2011 (2011-04-01), pages 1 - 81, XP055773063 * |

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| Publication number | Priority date | Publication date | Assignee | Title |
|---|---|---|---|---|
| CN112415107A * | 2021-01-21 | 2021-02-26 | 珠海润都制药股份有限公司 | Method for detecting impurities in sartan drug synthesis |
| Family To Family Citations | | | | |
| CN111072581A * | 2018-10-22 | 2020-04-28 | 珠海润都制药股份有限公司 | Valsartan free of genotoxic impurities and preparation method thereof |
| CN109574943A * | 2018-12-24 | 2019-04-05 | 浙江工业大学上虞研究院有限公司 | The preparation method of Valsartan nitrous clout |
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* Cited by examiner, † Cited by third party, ‡ Family to family citation

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| Publication | Publication Date | Title |
|---|---|---|
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| | | |
| US20190359605A1 | 2019-11-28 | Co-crystals of sglt2 inhibitors, process for their preparation and pharmaceutical compositions thereof |
| JP7086118B2 | 2022-06-17 | L-ornithine phenylacetate and its manufacturing method |
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| JP2001002657A | 2001-01-09 | Production of 2-alkyl-4-chloro-5-hydroymethylimidazole derivative |

## Priority And Related Applications

### Priority Applications (3)

| Application | Priority date | Filing date | Title |
|---|---|---|---|
| CN201880094671.5A | 2018-07-13 | 2018-07-17 | Synthesis method of valsartan |
| EP18926265.2A | 2018-07-13 | 2018-07-17 | Method for synthesizing valsartan |
| US17/259,292 | 2018-07-13 | 2018-07-17 | Method for synthesizing valsartan |

### Applications Claiming Priority (2)

| Application | Filing date | Title |
|---|---|---|
| CN201810771261.1 | 2018-07-13 | |
| CN201810771261 | 2018-07-13 | |

### Legal Events

| Date | Code | Title | Description |
|---|---|---|---|
| 2020-02-26 | 121 | Ep: the epo has been informed by wipo that ep was designated in this application | **Ref document number**: 18926265<br>**Country of ref document**: EP<br>**Kind code of ref document**: A1 |
| 2021-01-14 | NENP | Non-entry into the national phase | **Ref country code**: DE |
| 2021-02-19 | ENP | Entry into the national phase | **Ref document number**: 2018926265<br>**Country of ref document**: EP |

**Effective date**: 20210215

## Concepts

machine-extracted

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| Name | Image | Sections | Count | Query match |
|---|---|---|---|---|
| C09CA03 - Valsartan | | title,claims,abstract,description | 260 | 0.000 |
| valsartan | | title,claims,abstract,description | 260 | 0.000 |
| synthesizing | | title,claims,abstract,description | 25 | 0.000 |
| Valsartan | | title,claims,abstract | 20 | 0.000 |
| layer | | claims,abstract,description | 129 | 0.000 |
| water | | claims,abstract,description | 69 | 0.000 |
| organic layer | | claims,abstract,description | 63 | 0.000 |
| azide | | claims,abstract,description | 48 | 0.000 |
| solvent | | claims,abstract,description | 47 | 0.000 |
| quenching | | claims,abstract,description | 46 | 0.000 |
| impurity | | claims,abstract,description | 44 | 0.000 |
| valsartan methyl ester | | claims,abstract,description | 38 | 0.000 |
| quenching | | claims,abstract,description | 32 | 0.000 |
| DMNA | | claims,abstract,description | 27 | 0.000 |
| acid | | claims,abstract,description | 25 | 0.000 |
| sodium chloride | | claims,abstract,description | 20 | 0.000 |
| drying | | claims,abstract,description | 19 | 0.000 |
| extraction | | claims,abstract,description | 15 | 0.000 |
| acidificating | | claims,abstract,description | 11 | 0.000 |
| filtration | | claims,abstract,description | 9 | 0.000 |
| reaction mixture | | claims,abstract,description | 8 | 0.000 |
| alkali | | claims,abstract,description | 7 | 0.000 |
| salts | | claims,abstract,description | 5 | 0.000 |
| hydrolyzing | | claims,abstract,description | 3 | 0.000 |
| acetic acid ethyl ester | | claims,description | 234 | 0.000 |
| stirring | | claims,description | 109 | 0.000 |
| chemical reaction | | claims,description | 103 | 0.000 |
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| N,N-dimethylformamide | | claims,description | 57 | 0.000 |
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| aqueous solution | | claims,description | 50 | 0.000 |
| sodium chloride | | claims,description | 47 | 0.000 |
| sodium hydroxide | | claims,description | 45 | 0.000 |
| crystallisation | | claims,description | 35 | 0.000 |
| crystallization | | claims,description | 35 | 0.000 |

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| mixture | claims,description | 32 | 0.000 |
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| sodium azide | claims,description | 30 | 0.000 |
| methylene dichloride | claims,description | 26 | 0.000 |
| Sodium nitrite | claims,description | 24 | 0.000 |
| Sulfuric acid | claims,description | 15 | 0.000 |
| MeOtBu | claims,description | 14 | 0.000 |
| Zinc chloride | claims,description | 14 | 0.000 |
| mgso4 | claims,description | 14 | 0.000 |
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| sodium nitrite | claims,description | 12 | 0.000 |
| washing | claims,description | 12 | 0.000 |
| na2so4 | claims,description | 9 | 0.000 |
| Anisole | claims,description | 8 | 0.000 |
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| Sodium hypochlorite | claims,description | 8 | 0.000 |
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| potassium hydroxide | claims,description | 8 | 0.000 |
| xylene | claims,description | 8 | 0.000 |
| 1-butoxybutane | claims,description | 7 | 0.000 |
| brine | claims,description | 7 | 0.000 |
| hydron;triethylazanium;sulfate | claims,description | 7 | 0.000 |
| sodium sulfate | claims,description | 7 | 0.000 |
| sodium sulphate | claims,description | 7 | 0.000 |
| Potassium azide | claims,description | 6 | 0.000 |
| acetone | claims,description | 6 | 0.000 |
| nitrite anion | claims,description | 6 | 0.000 |
| pyridin-1-ium;chloride | claims,description | 6 | 0.000 |
| OP(O)(O)=O.CN1CCCCC1 | claims,description | 5 | 0.000 |
| hydrolysis reaction | claims,description | 5 | 0.000 |
| iso-propanol | claims,description | 5 | 0.000 |
| triethylamine | claims,description | 5 | 0.000 |
| Hypobromite | claims,description | 4 | 0.000 |
| Hypochlorite | claims,description | 4 | 0.000 |

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| OS([O-])(=O)=O.C[NH+]1CCCCC1 | claims,description | 4 | 0.000 |
| OS([O-])(=O)=O.C[NH+]1CCOCC1 | claims,description | 4 | 0.000 |
| P(=O)(O)(O)O.CN1CCOCC1 | claims,description | 4 | 0.000 |
| S(=O)(=O)(O)O.C(C)(C)N(CC)C(C)C | claims,description | 4 | 0.000 |
| desiccant | claims,description | 4 | 0.000 |
| dihydrogen phosphate;triethylazanium | claims,description | 4 | 0.000 |
| dihydrogen phosphate;trimethylazanium | claims,description | 4 | 0.000 |
| ethanol | claims,description | 4 | 0.000 |
| hydron;trimethylazanium;sulfate | claims,description | 4 | 0.000 |
| n-methylmorpholine | claims,description | 4 | 0.000 |
| potassium chloride | claims,description | 4 | 0.000 |
| pyridine | claims,description | 4 | 0.000 |
| ring formation reaction | claims,description | 4 | 0.000 |
| 1-methylpyrrolidine;sulfuric acid | claims,description | 3 | 0.000 |
| Calcium hypochlorite | claims,description | 3 | 0.000 |
| N,N-diethylethanamine;sulfate | claims,description | 3 | 0.000 |
| calcium;dihypobromite | claims,description | 3 | 0.000 |
| hydron;2H-tetrazole | claims,description | 3 | 0.000 |
| magnesium chloride | claims,description | 3 | 0.000 |
| metal | claims,description | 3 | 0.000 |
| metal | claims,description | 3 | 0.000 |
| phosphoric acid;pyridine | claims,description | 3 | 0.000 |
| sodium;hypobromite | claims,description | 3 | 0.000 |
| 1-heptoxyheptane | claims,description | 2 | 0.000 |
| 1-methylpiperidine | claims,description | 2 | 0.000 |
| 1-methylpyrrolidine | claims,description | 2 | 0.000 |
| Carbonate dianion | claims,description | 2 | 0.000 |
| Diphenyl ether | claims,description | 2 | 0.000 |
| Lewis acid | claims,description | 2 | 0.000 |
| Lithium azide | claims,description | 2 | 0.000 |
| N-ethyl-N-propan-2-ylpropan-2-amine;phosphoric acid | claims,description | 2 | 0.000 |
| O.O.[Cl-].[Cl-].[Zn+2] | claims,description | 2 | 0.000 |
| P(=O)(O)(O)[O-].C[NH+]1CCCC1 | claims,description | 2 | 0.000 |
| Potassium nitrite | claims,description | 2 | 0.000 |
| Titanium tetrachloride | claims,description | 2 | 0.000 |
| Tributyltin chloride | claims,description | 2 | 0.000 |
| Trimethylamine | claims,description | 2 | 0.000 |
| cacl2 | claims,description | 2 | 0.000 |
| calcium chloride | claims,description | 2 | 0.000 |

| | | | |
|---|---|---|---|
| calcium chloride | claims,description | 2 | 0.000 |
| cesium;azide | claims,description | 2 | 0.000 |
| diisopropyl ether | claims,description | 2 | 0.000 |
| filter cake | claims,description | 2 | 0.000 |
| hydroxyl anion | claims,description | 2 | 0.000 |
| lewis acids | claims,description | 2 | 0.000 |
| potassium chloride | claims,description | 2 | 0.000 |
| potassium chloride | claims,description | 2 | 0.000 |
| potassium nitrite | claims,description | 2 | 0.000 |
| potassium nitrite | claims,description | 2 | 0.000 |
| potassium nitrite | claims,description | 2 | 0.000 |
| pyridine;sulfate | claims,description | 2 | 0.000 |
| pyridine;sulfuric acid | claims,description | 2 | 0.000 |
| reaction time | claims,description | 2 | 0.000 |
| sulfuric acid derivatives | claims,description | 2 | 0.000 |
| tetrazolyl group | claims,description | 2 | 0.000 |
| triethylazanium;chloride | claims,description | 2 | 0.000 |
| diethyl ether | claims | 4 | 0.000 |
| 1-methoxy-2-methylbenzene | claims | 1 | 0.000 |
| 1-methoxybutane | claims | 1 | 0.000 |
| S(=O)(=O)([O-])[O-].C[NH+]1CCCC1.C[NH+]1CCCC1 | claims | 1 | 0.000 |
| Silicon tetraazide | claims | 1 | 0.000 |
| Trimethylsilyl azide | claims | 1 | 0.000 |
| chloride salts | claims | 1 | 0.000 |
| cooling | claims | 1 | 0.000 |
| hexane | claims | 1 | 0.000 |
| metal chloride | claims | 1 | 0.000 |
| mineralic acids | claims | 1 | 0.000 |
| organic solvent | claims | 1 | 0.000 |
| tolyl group | claims | 1 | 0.000 |
| method | abstract,description | 36 | 0.000 |
| toxic | abstract,description | 6 | 0.000 |
| toxic | abstract,description | 6 | 0.000 |
| drug | abstract,description | 4 | 0.000 |
| active ingredient | abstract | 1 | 0.000 |
| diluting | abstract | 1 | 0.000 |
| regulatory | abstract | 1 | 0.000 |

Show all concepts from the description section